UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,191	10/24/2001	Avi J. Ashkenazi	39780-2630.062 US C	6712

7590 07/07/2004

Ginger R. Dreger
Heller Ehrman White & McAuliffe LLP
275 Middlefield Road
Menlo Park, CA 94025

EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,191	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3-25-02, 9-3-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS 4-28-03*.

DETAILED ACTION

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e), 120 and 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Applicant's have amended the first line of the specification as directed in the preliminary amendment submitted 8-4-03. The amendment identifies multiple US serial numbers, PCT international applications and provisional applications. Applicant's have also submitted a supplemental communication of 6-21-02 that provides a priority map and identifies particular applications in which PRO320 (SEQ ID NO's:118 and 119) is allegedly disclosed. The map notes that the first disclosure is within US provisional 60/078,004. These sequences are found in this priority application. However, utility is granted based upon activity in EXAMPLE 109: Ability of PRO Polypeptides to Inhibit Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assay 9) at p. 326. However, support for activity in this assay is not found in the priority applications until the filing of PCT/US99/05028, filed 3-8-99. As priority is not

found until the 3-8-99 filing date, this application has been examined with the effective filing date of 3-8-99. Priority cannot be granted where no support for the activity of the noted sequences is provided.

Should the Applicant disagree with the Examiner's factual determination above, it is incumbent upon the Applicant to provide the serial number and specific page numbers of any parent application filed prior to 3-8-99 which specifically supports the claim limitations for each and every claim limitation in all the pending claims which Applicant considers to have been in possession of and fully enabled prior to 3-8-99.

Utility

2. Utility is established based upon EXAMPLE 109: Ability of PRO Polypeptides to Inhibit Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assav 9) at p. 326 of the specification.

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 58-77 are rejected under 35 U.S.C. 112, first paragraph, as

containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes a polynucleotide consisting of SEQ ID NO:118 encoding the peptide sequence consisting of SEQ ID NO:119, which is shown to have activity in EXAMPLE 109: Ability of PRO Polypeptides to Inhibit Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assav 9) at p. 326. However, the claims as written include polynucleotides encoding polypeptides having at least 80-99% sequence identity with SEQ ID NO:119 and polypeptides including or lacking various regions including; lacking its signal peptide, encoding the extracellular domain, encoding the extracellular domain but lacking its signal peptide, as well as sequences which hybridize to these regions, but for which no particular biological activity or function is recited. Thus, the claims are directed to various genus' defined solely by homology and hybridization comparison.

However, the instant disclosure of a single polypeptide, that of SEQ ID NO:119 with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must

describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the

genus.

However, the instant specification discloses only the single sequence and no other members of the claimed genus. Given the unpredictability of homology comparisons, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000 and the fact that the specification fails to provide objective evidence of any additional sequences with the same requisite function, it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences and there is no evidence for a correlation or nexus provided between possession of any homologous feature and the activities of EXAMPLE 109: Ability of PRO Polypeptides to Inhibit Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assav 9) at p. 326 such that it is clearly conveyed that possession of any polypeptide having such structural similarity would possess the same function. Thus, the claims lack adequate written description support.

6. Claims 58-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:118 which encodes SEQ ID NO:119 exemplified as exhibiting activity EXAMPLE 109: Ability of PRO Polypeptides to Inhibit Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assav 9) at p. 326, does not reasonably provide enablement for the variable polynucleotide and peptide sequences and for such generic sequences where no requisite functional activity is provided as claimed. The specification does not enable any person skilled in the art to which

it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of conserved structural components to both biological function and immunological recognition.

Instant specification discloses a single PRO320 sequence that differs from the other sequences disclosed. The specification notes that the peptide exhibits activity in EXAMPLE 109: Ability of PRO Polypeptides to Inhibit Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assav 9) at p. 326. However, the specification fails to note such conserved activities in any 80-99% variable molecule. However, applicants

claims are directed to polynucldoetides encoding peptides with 80-99% homology, to extracellular domains, to sequences lacking the signal peptide and to hybridizing sequences where no requisite function is required.

The specification does not enable this broad scope of the claims that encompasses a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that the polypeptides retain sufficient structural similarity to evoke activity. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful and the skilled artisan would not necessarily expect functional conservation among homologous sequences. Moreover, no similar function is required of the additional sequences. The artisan would be unable to determine how to use such similar sequences that lack common function. The additional members would require further experimentation to discover their requisite use. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Thus, in view of the quantity of experimentation necessary, the lack of

working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims the artisan cannot make and use the invention without undue experimentation.

7. Claims 58-77 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the deposit of ATCC 209670. Because it is not clear that cell lines possessing the properties of ATCC 209670 are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the claims require the use of ATCC 209670, a suitable deposit for patent purposes is required. Accordingly, filing of evidence of the reproducible production of the cell line claimed in claims 58-77 is required. Without publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the cell line is an unpredictable event.

There is insufficient assurance that all required deposits have been made and all the conditions of 37 CFR § 1.801-1.809 have been met.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority

under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of the patent on this application. These requirements are necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR § 1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;

2) The name and address of the depositor;

3) The date of deposit;

4) The identity of the deposit and the accession number given by the depository;

5) The date of the viability test;

6) The procedures used to obtain a sample if the test is not done by the depository; and

7) A statement that the deposit is capable of reproduction.

As a means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the ATCC 209670 cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR § 1.801-1.809 for further information concerning deposit practice.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 58-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 58-77 are directed to isolated peptides comprising "the extracellular domain" and "lacking its associated signal peptide". Page 122, lines 12-15 of the specification generally teaches that the PRO "extracellular domains" are a form of the PRO polypeptide "which is essentially free of the transmembrane and cytoplasmic domains." Figure 44-45 teaches that PRO320 possesses a "Signal peptide" at amino acids 1-21, EGF-like domain cysteine pattern signature at amino acids 80-91 and a calcium-binding EGF-like domain at amino acids 103-124, 230-251 and 185-206. However, these limitations cannot be read into the claims and the specification fails to teach the orientation of the

molecule with respect to the intracellular and/or extracellular portions. Further, the claim is directed to the extracellular domain lacking its associated signal peptides. However, signal peptides are not generally considered to be "associated with" extracellular domains and indeed in this particular incidence they are not adjacent as identified. Thus, the metes and bounds of the recitations are indefinite with respect to those residues that are intended to be included or excluded by the claim recitations and the artisan is not provided definitive guidance whereby the residues may be determined.

Moreover, the claims are drawn to hybridizing sequences and to hybridization under stringent conditions. However, hybridization is variable depending on the conditions, see in particular Sambrook et al., Cold Spring Harbor Labs 1989, pp. 9.47-9.51 and 11.48-11.49. Those conditions that are deemed to be "stringent" vary in the art and are undefined in the specification. Accordingly, the metes and bounds of the residues included or excluded by the noted recitations is indefinite. Clarification of the particular amino acids and hybridization conditions are required.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an

application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 58-77 are rejected under 35 U.S.C. 102(e) as being anticipated by Ford et al., US Patent No. 6,392,018 filed 2-12-1999 and issued May 21, 2002.

Ford et al., teach EGF Motif protein obtained from fetal liver-spleen cDNA library, see in particular title, abstract. The protein is distinguished by Ford as SEQ ID NO:19 bearing 100% similarity to instant SEQ ID NO:119 encoded by SEQ ID NO:118. The signal sequence is taught at column 1, lines 18-39, column 5, lines 49-59, Figure 5, and column 9, lines 20-26. The extracellular portion is noted for example at column 6-7, paragraph spanning, column 9, lines 46-50, and column 10, lines 16-25 denoted by "soluble" portions as described at column 11, lines 5-12, having transmembrane and intracellular portions deleted, also signal sequences deleted or mature forms are noted at column 10, lines 16-25. Also discussed are hybridizing and variable sequences (80-99%) as noted at column 12, line 50-column 13, line 49. Ford further denotes vectors, host cells and suitable methods for expression, see in particular columns 13-21, for example. Thus, the reference teachings anticipate the claimed invention.

Status of Claims

12. No claims are allowed.

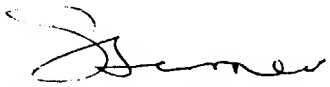
13. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November

15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (571) 272-0887.



Sharon L. Turner, Ph.D.
June 22, 2004